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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,480	MACKAY, CHARLES REAY	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10,13-20,22,27,28,30-35 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10,13-20,22,27,28,30-35 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-4-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 6, 7, 9, 11, 12, 21, 23-26, 29, 36-39 and 41 have been canceled. Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 remain pending.

Applicant's arguments filed 3-10-09 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Please do not use bold face type in amendments.

Specification

The title of the invention will have to be changed to more closely reflect the claims.

Claim Rejections - 35 USC § 101

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 remain rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The claims are directed to a transgenic rodent having a polynucleotide encoding a human C5aR or humanized C5aR. Specifically, claims 2 and 3 require the human C5aR has an amino acid sequence of SEQ ID NO: 3 or a nucleic acid sequence of SEQ ID NO: 3

C5aR

C5a binds C5a receptor (C5aR) (pg 1, line 28).

Morgan (WO 95/00164) taught human C5a is one of the best described and most potent proinflammatory mediators derived from the complement system. Morgan states

C5a possess multiple biologic activities that relate to host defense and may play a role in inflammatory disease processes.

Since the time of filing, Lee (Nature Biotech., Oct. 2006, Vol. 24, No. 10, pg 1279-1284) taught C5a binding C5aR facilitates leukocyte chemotaxis and release of inflammatory mediators (abstract), which is not disclosed in the instant specification. In fact in 2007, Monk (British J. Pharm., 2007, Vol. 152, pg 429-448) taught the function of C5aR was previously misunderstood and the understanding of the physiology of C5a improved by using knockout and knockin mice (pg 429, abstract).

The specification and the art at the time of filing do not disclose any diseases affected by C5a binding to C5aR or by C5aR mutations in humans.

Using the mice as models of disease

The specification teaches making mice with a disruption in endogenous C5aR replaced with normal human C5aR (Examples 1-5). The mice described by applicants and claimed in the instant application are not models for disease because the mice do not have mutated human C5aR and because the specification does not teach mice expressing normal human C5aR correlate to any disease found in humans. Furthermore, the specification and the art at the time of filing do not disclose any diseases affected by C5a binding to C5aR or by C5aR mutations in humans. The role of C5a/C5aR in disease in humans is not disclosed in the specification and remains unknown in the art. Applicants have provided no guidance that the knockin correlates to a naturally occurring mutation found in humans or that the mice have a phenotype that

models a disease. Without such guidance, the mice cannot be used as models of disease.

Using the mice to identify compounds that modulate C5aR

The specification teaches using the knockin mice to screen anti-inflammatory compounds (pg 7, lines 23-30; pg 59, line 23). The knockin mice were subjected to sera from a K/BxN model of rheumatoid arthritis; K/BxN mice express a transgene encoded T cell receptor (TCR) reactive to a self-peptide derived from the ubiquitously expressed glycolytic enzyme GPI, wherein the mice spontaneously develop arthritis (pg 59, lines 26-36). Sera from arthritic K/BxN mice was injected intraperitoneally into H5Rf/H5Rf knockin mice (pg 61, lines 16-21). The mice develop signs of inflammation indicating the human C5aR is expressed and the receptor is processed correctly to the G-protein signaling system (pg 61, lines 24-26; pg 62, lines 4-9). The specification states:

"The human C5aR knock-in mice were developed as a useful tool to screen anti-human C5aR compounds for anti-inflammatory activity. To test the utility of the mice we administered both homozygous hC5aR and wild-type (control) mice an antibody specific for human C5aR (it does not bind to mouse C5aR) or a control antibody (same isotype but irrelevant specificity) in the K/BxN model and determined the effect of the antibody on inflammatory disease progression. The antibody was injected i.p. twice (200 ug per dose), one day before and one day following the first K/BxN serum injection. Mice were monitored as described above." (pg 62, lines 20-27)

It is unclear how the "homozygous hC5aR and wild-type (control) mice" are "in the K/BxN model" as described by applicants; the specification does not clearly set forth that knockin mice and wild-type mice were both given K/BxN sera. Second, it was predetermined that the anti-human C5aR antibody targeted hC5aR and not mouse

C5aR, so the controls required to identify compounds that specifically target hC5aR using the mice claimed are not described by applicants. Applicants have left those skilled in the art with no information how to use the non-human mammals claimed to identify compounds that target human C5aR. Finally, merely observing whether a compound known to specifically target human C5aR decreases inflammation in a knockin mouse (given K/BxN sera?) as compared to a control is not substantial. Therefore, the alleged use - using the knockin to screen anti-inflammatory compounds already known to target human C5aR - is so general as to be meaningless. As such, applicants have merely provided a starting point for further research and not provided an end point of a research effort in determining how to identify compounds of interest using the knockin claimed.

Conclusion

Overall, the knockin non-human mammals claimed do not correlate to "research tools" known to have patentable utility. For example, gas chromatographs separate the chemical components of a compound and identify them. Screening assays have various functions, but may be used, for example, to determine the amount of protein expression in a population of cells. Sequencing methods provide the nucleotide sequence of a nucleic acid molecule. Unlike gas chromatographs, screening assays or sequencing methods, the mice claimed are capable of providing data, but the may not reveal the function of the gene or provide any substantially useful information. For example, applicants injected a knockin mouse of the invention (injected with K/BxN sera?) an anti-human C5aR antibody and observed inflammation was decreased in the

mouse without determining the link between C5aR and disease. Nor did applicants identify agents that specifically target human C5aR using the knockin. Further research would be required to determine the role of human C5aR in disease, how to use the knockin as a model of disease or to identify agents capable of targeting human C5aR. The utility guidelines state using a product for further research is not a "substantial" utility.

The methods and cells claimed are included because they relate to making and using the knockin non-human mammals.

Response to Arguments

Applicants argue C5a was known to be a potent inflammatory molecule. Applicants point out that certain diseases are considered to be the result of uncontrolled C5a/C5aR signaling. Therefore, it appears applicants conclude that rodents having human C5aR are useful. Applicants' argument is not persuasive. Pg 7, lines 23-30, suggest using the rodent claimed to screen for drugs, but that asserted utility is specifically addressed above and is not substantial. The specification and the art at the time of filing do not disclose any diseases affected by C5a binding to C5aR or by C5aR mutations in humans.

Applicants point to pg 2, lines 9-18, which teach agonists of C5aR treat cancer. However, the specification does not teach how to use the rodent claimed as a model of cancer. Applicants do not teach one cancer that is affected by C5a binding to C5aR or by C5aR mutations in humans.

Applicants fail to elucidate the role of C5aR in any specific disease.

Applicants argue the rodents claimed are models of disease (pg 9 of the response filed 3-10-09). Applicants support the assertion by pointing to Example 6 which screens compounds that modulate inflammatory response using knockin C5aR mice. Applicants' argument is not persuasive. The mice described by applicants and claimed in the instant application are not models for disease because the mice do not have mutated human C5aR and because the specification does not teach mice expressing normal human C5aR correlate to any disease found in humans. Screening for compounds that modulate the inflammatory response can also be performed using wild-type mice. Applicants cite Monk but fail to point out what the C5aR knockin mice model. Overall, applicants have not described how the mice claimed model disease.

Applicants argue the rodents claimed can be used to screen for compounds that modulate C5aR as supported in Example 6 (pg 12). Applicants' argument is not persuasive for reasons in the basis of the rejection that specifically address Example 6.

Claim Rejections - 35 USC § 112

Enablement

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Upon overcoming the above rejection, the claims would also be subjected to a scope rejection. Claims 1-5, 8, 10, 12, 14-20, 22, 27, 28, 30-35 and 40 currently

encompass making any knockin rodent; however, the specification does not teach how to make any other rodent by teaching the protocols for making other rodent knockins or the cDNA of other rodents other than mice. Accordingly, the claims should be limited to knockin mice.

Claim Rejections - 35 USC § 103

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sato (Thrombosis and Haemostasis, 1999, Vol. 82, No. 2, pg 865-869), Roebroek (Methods in Molecular Biology, 2003, Vol. 209, 187-200), Homanics (2002, Methods in Alcohol related neuroscience research, Editor, Liu, Yuan, pg 31-61), Lester (Current Opin. Drug Discovery and Development, 2003, Vol. 6, No. 5, pg 633-639), Champtiaux (Current Drug Targets-CNS & Neurological Disorders, 2002, Vol. 1, pg 319-330), Girardi (J. Clin. Invest., Dec. 2003, Vol. 112, No. 11, pg 1644-1654) in view of Burmer (WO 02/61087-A2) for reasons of record.

Sato taught a knock-in mouse had an endogenous gene replaced with an exogenous gene or a mutant form of the endogenous gene (pg 866, col. 1, Gene Knock-in). Roebroek taught various strategies for making knockin mice and provided numerous references prior to applicants effective filing date that describe disrupting an endogenous mouse gene and replacing it with the human homologous cDNA (pg 188, 2.2; pg 190-191, 3.1). One example of a receptor mouse known at the time of filing was Homanics who taught disrupting a mouse receptor gene and replaced with homologous human receptor cDNA. Other examples of receptor knockin mice are described by Lester and Champtiaux. Cells were isolated from the mice, and compounds were

administered to the mice for pharmacokinetic evaluation. Sato, Roebroek, Homanics, Lester, Champtiaux did not disrupt the mouse C5aR gene and replace it with human C5aR cDNA.

However, knocking out the mouse C5aR gene in a mouse was known in the art at the time of filing as described by Girardi. Furthermore, human C5aR cDNA was known in the art at the time of filing as described by Burmer (SEQ ID NO: 79).

Thus it would have been obvious to those of ordinary skill in the art at the time the invention was made to make a humanized receptor knockin mouse as was well known in the art at the time of filing using the human C5aR cDNA of Burmer. Those of ordinary skill in the art at the time the invention was made would have been motivated to replace the mouse C5aR gene with human C5aR cDNA to test the functional redundancy of the gene, i.e. to test whether or not the exogenous gene can replace the function of the endogenous gene.

Applicants argue those of skill would not have had a reasonable expectation of success in making a knockin C5aR mouse using the combined teachings of Sato, Roebroek, Homanics, Lester, Champtiaux, Gerardi and Burmer. Applicants argue those of skill would not predict whether mouse C5a would bind to the human C5aR in vivo or cause chemotaxis of leukocytes in vivo. Applicants' argument is not persuasive. First, applicants' assertion of unpredictability appears to be an argument of unexpected results; however, applicants' assertion of unexpected results is unfounded. Without evidence to the contrary, the results obtained are expected. Second, the claims do not require the human C5aR binds mouse C5a or chemotaxis of leukocytes. Finally, those

of ordinary skill in the art at the time of filing would have had a reasonable expectation of successfully expressing human C5aR in a mouse with a disruption in the endogenous C5aR gene, which is all that is required.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Patent Examiner